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Management of anti-colton^{a} alloimmunisation in pregnancy: a case report

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Running title: Anti-Co^{a} alloimmunisation in pregnancy

Diagnosis and management of anti-Co^a alloimmunisation during pregnancy is a rare and challenging condition. Only five cases have been described up to now, four in the 1970s and one in 2008, but diagnosis and management has changed in the meantime (Smith, Stratton et al. 1970, Simpson 1973, McIntyre, Finigan et al. 1976, Fuhrmann, Kloppenburg et al. 1979, Michalewska, Wielgos et al. 2008). We here present such a case, its management and favourable outcome.

Alloimmunisation of a Co^a negative pregnant woman, carrying a Co^a positive fetus, may cause haemolytic disease in the fetus and newborn (HDFN) (Smith, Stratton et al. 1970, McIntyre, Finigan et al. 1976, Michalewska, Wielgos et al. 2008). Today, monitoring is performed by laboratory testing of antibody titer, although it is unknown whether antibody titration is helpful (de Haas, Thurik et al. 2015). Of greater importance are doppler flow measurements of the peak systolic velocity of the middle cerebral artery (MCA-PSV) (Zimmerman, Carpenter et al. 2002, Michalewska, Wielgos et al. 2008, Moise and Argoti 2012, de Haas, Thurik et al. 2015). In cases of fetal anaemia, intrauterine blood transfusion (IUT) by cordocentesis is established, challenged by the allocation of compatible blood (de Haas, Thurik et al. 2015).

A 32-year-old woman (blood group 0 RhD-, RhC-, Rhc+, RhE-, Rhe+, K-, Co^a-) was admitted to our hospital at 20+3 gestational weeks (gw) with an alloimmunisation against blood group antigen Co^a with increasing antibody titer. Antibody identification was performed by indirect antiglobulin testing (IAT) and enzyme (papain) testing using an in-house panel and Coombs and neutral cards (IAT/ID and papain/ID) (BioRad, Cressier, Switzerland) (Table 1a). Titration was performed in IAT/ID using a Co^a heterozygous test cell. A Co^a antigen determination of the fetus` father, using IAT/ID and non-commercial anti-Co^a and anti-Co^b sera, showed that he was Co^a homozygous. Monitoring of the fetus was performed every one to two weeks by MCA-PSV

measurements (Table 1b). Between 28 and 32 gw the MCA-PSV gradually increased with values above the 95th percentile and a Monocyte Monolayer Assay (MMA) showed a value of 29% (Nance, Nelson et al. 1989), so that anaemia was suspected and fetal transfusion planned. We used Co^{a}-, RhD-, RhC-, RhE-and Kell negative blood from a donor, as women between 0 and 50 years of age should be transfused with Rh/K phenotype compatible blood only, according to the Swiss recommendations. We did not use blood from the mother, as autologous blood donation during pregnancy is not a common, but rarely performed procedure in Switzerland, especially in order to avoid lowering the mother`s haemoglobin level. At 32+4 gw a cordocentesis was performed. An immediate intrauterine transfusion was initiated already before the fetal blood result was present, in order to avoid a possible second cordocentesis due to a dislocated needle. Knowing the haemoglobin/haematocrit of the fetus and of the preserved blood for transfusion, one can calculate the amount of blood needed to reach an appropriate fetal haemoglobin/haematocrit, according to the reference values by Mari (Mari, Deter et al. 2000). As the intraoperative blood results showed a haemoglobin and haematocrit of 123 g L-1 and 35.5 %, respectively, transfusion was stopped. So far, 40 ml of RhD-, RhC-, RhE-, Kell- and Co^{a} negative, irradiated and washed red blood cells, depleted for plasma and leucocytes, with a haematocrit of 81.3 % were transfused, leading to a posttransfusion haemoglobin level and haematocrit of 168 g L-1 and 48.7 %, respectively. MCA-PSV decreased to normal values within minutes and remained stable (Table 1b). Delivery was performed at 37+2 gw by elective cesarean as part of our standard protocol for alloimmunised pregnancies. Blood testing of the newborn confirmed blood group A RhD negative with antibodies against Co^{a}, detected by direct antiglobulin testing (DAT) (agglutination ++, eluate testing positive). Fetal umbilical cord haemoglobin and haematocrit levels were 156 g L-1 and 47%, respectively (Table 1a). Due to fetal hyperbilirubinaemia on the fifth day postpartum, the neonate was

treated with phototherapy for three days (Table 1a). This was the reason, why mother and child were discharged from hospital not before eight days postpartum, both without complications.

Given the limited data on the relevance of antibody titer, close monitoring of the mother and fetus was justified. Repeated antibody screening was performed for early detection of a titer increase. Although a significant increase in antibody titer was documented, this did not reflect fetal anaemia. Unfortunately, a clear cutoff for anti- Co^{a} antibody titers, leading to fetal anaemia, is lacking (de Haas, Thurik et al. 2015). In our and other cases of severe fetal anaemia, the antibody titer was measured at a level of 1:128 in IAT and in a case of mild HDFN the titer was only 1:32 (Simpson 1973, McIntyre, Finigan et al. 1976, Michalewska, Wielgos et al. 2008). Here, however, it is important to consider the different methods of antibody titer determination used in the 1970s and nowadays. Additionally, a MMA can be performed to evaluate the clinical significance of the antibody. Monocyte reactivity greater than 20% was initially reported to correlate with needs for transfusion (Nance, Arndt et al. 1987). Subsequent studies from the same author, however, indicated that the assay may not always predict the outcome of the infant, as seen in our case, and should not be used to evaluate HDFN. Before diagnosing fetal anaemia by MCA-PSV, bilirubin extinction in amniotic fluid from amniocentesis was performed (Moise and Argoti 2012, de Haas, Thurik et al. 2015). This method was used in the four cases in the 1970s, but required repeated amniocentesis with the risks of an invasive procedure (Simpson 1973, McIntyre, Finigan et al. 1976, Fuhrmann, Kloppenburg et al. 1979). Measurement of the MCA-PSV is the gold standard nowadays and was performed in our and Michalewska`s case (Mari, Adrignolo et al. 1995, Michalewska, Wielgos et al. 2008). Compared to that case, where MoM-values for the MCA-PSV cutoff were used, we used the reference values

published by Kurmanavicius (Mari, Adrignolo et al. 1995, Kurmanavicius, Streicher et al. 2001). However, in our case MCA-PSV values indicative for fetal anaemia also exceeded the MoM-values by Mari. No neonatal exchange or top-up transfusion was required in our case and in the ones of McIntyre and Smith, but in the other cases (Table 2). Although MCA-PSV values were indicative for fetal anaemia in our case, blood values were almost normal for the age of gestation.

The neonatal hyperbilirubinaemia, treated with phototherapy for three days, was probably not due to alloimmunisation against Co^{a}, but in the context of intensified postpartum haemolysis.

A great challenge in anti-Co^{a} alloimmunised patients is the allocation of compatible blood for transfusion. In Switzerland, this can be achieved by finding a donor through the "DGTI Rare Donor Register" (http://www.iblutspende.ch/rare-donors.html), by autologous donation of maternal blood or by transfusion of washed maternal erythrocytes (not a common procedure, limited to rare cases with missing compatible blood donors). In this case, the possible selection was even smaller due to the 0 RhD negative blood group of the patient (only 6% of blood donors). Only seven donors were compatible for the constellation RhD-, RhC, RhE-, K- and Co^{a} negative in Switzerland and only three of them available at that time. Furthermore, preparation time of two to three days had to be taken into consideration. Unfortunately, non-invasive treatment options are not available up to date.

Anti-Co^{a} alloimmunisation during pregnancy is a challenging situation. Both national and international blood donor registries are extremely helpful to identify compatible blood donors. Despite increased antibody concentrations, MCA-PSV and MMA, this case did not develop fetal or neonatal anaemia and did not require exchange transfusion after birth. Serologic methods can help to initiate fetal monitoring and

doppler MCA-PSV measurements might be helpful to avoid serial amniocentesis or fetal blood samplings, but can also be misleading in some cases.

Tables

154 Table 1:

155 a) Haematological course of mother and fetus/neonate

gestational weeks	anti-Co[a] titer	maternal haemoglobin (g/100mL)	maternal haematocrit (%)	fetal/neonatal haemoglobin (g/100mL)	fetal/neonatal haematocrit (%)	Neonatal blood bilirubin (mcmol/L)	neonatal transcutaneous bilirubin (mcmol/L)
6+3	2						
10+2	8	121	36				
13+2	16						
16+3	32						
20+3	128	129	37.6				
30+3	16						
32+4 (before transfusion)		127	37.5	123	35.5		
32+4 (after transfusion)				168	48.7		
37+1		122	35.3				
37+2 (cesarean)				156	47	39	59
1st day postpartum		117	35.8		56	105	109
2nd day postpartum					56	200	179
3rd day postpartum							225
4th day postpartum					55	276	241
5th day postpartum					56	300	
6th day postpartum					55	281	
7th day postpartum					61	299	
8th day postpartum					57	258	

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157 b) MCA-PSV values in the course of pregnancy

gestational weeks	MCA -PSV (cm/s)
20+3	27
22+3	32
24+3	39
26+3	45
28+3	54*
29+3	60*
29+6	60*
30+3	65*
30+5	61*
31+3	62*
31+6	74*
32+2	72*
32+4 (before transfusion)	72*
32+4 (after transfusion)	43
32+5	54
33+5	63
34+6	65
36+4	72

158 *Value above the 95th percentile of reference limits

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161 Table 2: Course and outcome of the six cases

Case	Anit-Co[a] titer	Amnicentesis (n)	Cord blood sampling (n)	Fetal anaemia	Intrauterine transfusion (n)	Neonatal anaemia	neonatal transfusion (n)
Smith 1970		0	0	none	0	none	0
Simpson 1973	128	2	0	severe	0	severe	2
McIntyre 1976	32	1	0	none	0	none	0
Fuhrmann 1979		2	0	mild	0	severe*	2*
Michalewska 2008	128	0	3	severe	1	severe	5
Our case	128	0	1	mild	1	mild	0

*due to bleeding out of a ruptured of vessel in presence of insertio velamentosa

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Contribution of the authors:

Nina Kimmich: Management and treatment of the patient, wrote the manuscript

Brigit Brand: Management of the patient, correction of the manuscript

Hein Hustinx: Management of the patient, correction of the manuscript

Adriana Komarek: Management of the patient, correction and translation of the manuscript

Roland Zimmermann: Management and treatment of the patient, correction of the manuscript

Disclosure of Interests

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